Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claims 1-6, 11-21, 23-26, 30-37, 42, 43, 64-67, and 73 have been canceled without prejudice. New claims 74-80 have been introduced. Descriptive support for claim 74 is provided in original claim 7. Descriptive support for claims 75-77 is provided in the description of the polynucleotide at Example 8. Descriptive support for claim 78 is provided at page 32, lines 7-9. Descriptive support for claims 79 and 80 is provided in Example 6. Descriptive support for the amendments to claim 7 is provided, *e.g.*, in Example 8 (*see* page 72, line 5) and page 34, lines 7 to page 35, line 12. Claims 38-41, 48-51, 55-60 are currently withdrawn but remain pending.

Applicants would like to request reconsideration of the restriction requirement, particularly as between the subject matter of sub-groups A and B (of Group II, as identified in Paper 4 imposing the restriction requirement). Sub-groups A and B represent the nucleic acid molecules encoding the tau and gamma subunits, respectively. As demonstrated in the present application, the tau subunit and gamma subunits (whether a -1 frameshift or a -2 frameshift product) are functionally and structurally similar. All of these subunits are naturally encoded by the same nucleic acid molecule that contains a frameshift site. (Clearly, as described at page 74, lines 11-17, recombinant nucleic acid molecules can be prepared that each encode only one of these subunits, but such nucleic acid molecules will be share high identity.) As shown in Figures 4A-F, the tau and gamma subunits are identical between residues 1-453 (out of 529 for tau), and are distinct only with respect to their C-terminal regions. All three of these subunits contain the conserved ATP-binding region and Zinc-finger domain as identified in the alignment shown in Figure 5 and the corresponding description of the figure. For this reason, applicants respectfully request withdrawal of the restriction as between sub-groups A and B of Group II.

Applicants further request reconsideration of the restriction as between sub-groups A, B, and C (of Group II). The relationship between the subject matter of subgroups A and B is described above. Subgroup C relates to the *dnaE* nucleic acid encoding the alpha subunit. In replying to applicants response to the restriction requirement, the U.S. Patent and Trademark Office ("PTO") indicated reluctance to join this subject matter together despite PTO policy to the contrary (*see* 1192 O.G. 68 (November 19, 1996), cited in response to restriction requirement) and the public interest in resolving any interfering subject in as

timely a manner as possible. Applicants have identified potentially interfering subject matter in U.S. Patent No. 6,238,905 to McHenry et al. ("McHenry"), and apparently the above-noted PTO policy was *followed* during prosecution of the underlying McHenry application because no such restriction occurred in that case. Thus, applicants are merely requesting that PTO restriction policy be followed in a *consistent* manner, particularly given the possibility for an interference in this instance.

In addition to all of the above, applicants further request an explanation as to why claims 38-41 were not examined when these were identified in Paper 4 as belonging to Group II. There has been no basis provided for their withdrawal, and therefore such withdrawal is improper. Applicants would like the PTO to consider the fact that SEQ ID NOs: 6 and 8, recited in claim 38, are two oligomers that were utilized in the cloning of *Thermus thermophilus dnaX* (*see* paragraph beginning at page 58, line 18, as amended in the amendment filed November 21, 2003). Because claims 38-41 relate to subject matter currently under examination, the withdrawal of these claims appears to be in error.

For all these reasons, applicants respectfully request that the restriction requirement be withdrawn at least in part.

The objections to the specification are respectfully traversed in view of the above amendments to the drawings and the specification. The objections should therefore be withdrawn.

The objections to the claims are respectfully traversed in view of the above amendments and the following remarks, and should therefore be withdrawn.

The rejection of claims 8-10 under 35 U.S.C. § 112 (second paragraph) for indefiniteness is respectfully traversed in view of the above amendments and the following comment. With respect to the rejection of claim 10, applicants submit that the above amendment to the drawing makes clear that SEQ ID NO: 1 is properly recited therein.

The rejection of claims 7-10, 11, 12, 22, 23, 28, 29, 30, 34, 44, 45, 52, 61, and 68-72 under 35 U.S.C. § 112 (first paragraph) as lacking written description support is rendered moot with respect to canceled claims, and is otherwise respectfully traversed in view of the above amendments.

The PTO has basically taken the position that the specification fails to teach any claimed sequences other than the *dnaX* sequence of SEQ ID NO: 1 (encoding tau subunit

of SEQ ID NO: 2), and that these species are not adequately representative of the claimed genus. In addition, the PTO asserts that the specification fails to teach any particular structural/activity relationship. Applicants disagree.

As acknowledged by the PTO, the present application provides a nucleotide sequence and protein sequence for *Thermus thermophilus dnaX* (i.e., SEQ ID NOs: 1 and 3 for the nucleotide sequence, and SEQ ID NO: 2 for the amino acid sequence). Contrary to the above-noted assertion, the present application does identify a structural/activity relationship for tau subunits encoded by *dnaX*. In particular, Figures 4A-F and 5 identify structural features shared by many diverse prokaryotic tau subunits. Hence, there are certain structural features that would be expected by one of ordinary skill in the art to be conserved among the presently claimed genera of claims 7 and 44 given that even members outside the scope of the claimed genus (such as the *E. coli dnaX*) possess these conserved structural features. In particular, as shown in Figure 5 and recited at page 72, lines 5-6, the consensus GXXGXGKT motif for nucleotide binding is conserved in all these protein products. This conserved structure is related to ATP-binding, and the encoded tau subunit has ATP-binding activity. Other structural features of the polynucleotide and encoded tau subunit are described in Example 8 on pages 71-75. Another generally conserved structural feature of tau subunits is a four-cysteine residue zinc-finger domain (*see* Figure 5). The disclosed *Thermus thermophilus* polynucleotide also contains a hepta-A frameshifting site whose sequence comports with known frameshift heptamers, and two Shine-Dalgarno sequences located upstream of the frameshifting site. Because one or more of the conserved structures would be expected to likewise be conserved among polynucleotides from other thermophilic bacterium, including *Thermus* species such as *Thermus thermophilus*, it is clear that the present application identifies a structure/activity relationship for tau subunits and their encoding nucleic acids.

With respect to claim 7 and claims 8-10, 22, 28, and 29 dependent thereon, this claim presently recites that the claimed genus includes polynucleotides that "hybridize[] to the complement of SEQ ID NO: 3 under hybridization and wash conditions comprising 5X SSC at 65°C." Given the structural and functional limitations presently recited in claim 7, applicants submit that the disclosure of the hybridization conditions and structure/activity relationship clearly indicates that applicants were in possession of the presently claimed genus at the time of filing.

With respect to claim 44 and claims 45, 52, 61, and 68-72 dependent thereon, applicants submit that the language recited in independent claim 44 is precisely the type of

claim language that was acknowledged in *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) as being acceptable under the written description requirement. In *Eli Lilly*, the Federal Circuit addressed the validity of several claims of U.S. Patent No. 4,652,525 to Rutter et al. ("Rutter"), specifically those claims that recited the limitations 'vertebrate,' 'mammalian,' or 'human' cDNA for insulin. Rutter disclosed the nucleotide and amino acid sequences of a rat cDNA encoding insulin, but merely described a general procedure for obtaining the human cDNA encoding insulin. *Id.* at 1567, 43 USPQ2d at 1405. The Federal Circuit found that the description of the rat cDNA did not provide adequate descriptive support for the narrow subgenus of 'human' cDNA (no species disclosed), the larger subgenus of 'mammalian' cDNA (only the one rat species disclosed), and the larger genus of 'vertebrate' cDNA (only the one rat species disclosed). *Id.* at 1567-68, 43 USPQ2d at 1405. The Federal Circuit did acknowledge, however, the district court's statement that the specification provided adequate written descriptive support for the subgenus of 'rat' cDNA encoding insulin. *Id.* at 1566.

Thus, functional language should be acceptable when the genus as claimed is sufficiently limited in scope (i.e., from *Thermus thermophilus*) and the specification describes one or more species within that genus. Claim 41 recites the same type of functional claim language that was identified as acceptable in *Eli Lilly* given the description of a single species by its nucleotide sequence. Thus, it should be evident that claim 41 and claims dependent thereon find written descriptive support in the present application.

For all these reasons, the rejection of claims 7-10, 22, 28, 29, 44, 45, 52, 61, and 68-72 as lacking written descriptive support is improper and should be withdrawn.

The rejection of claims 7-10, 11, 12, 22, 23, 28, 29, 30, 34, 44, 45, 52, 61, and 68-72 under 35 U.S.C. § 112 (first paragraph) as lacking enablement is rendered moot with respect to canceled claims, and it otherwise traversed with respect to the remaining claims.

All that is needed is objective enablement of what is claimed. *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In particular, the present application provides the nucleotide sequence of a *Thermus thermophilus dnaX* (e.g., SEQ ID NOs: 1 and 3) and describes how one of ordinary skill can isolate other homologs of the disclosed sequence (*see* page 34, line 7 to page 35, line 12; Example 1), express the tau subunits encoded by such homologous *dnaX* sequences (*see* Examples 2-6), and test the encoded tau subunit for activity (*see* Examples 6 and 8). Thus, one of ordinary skill in the art

would have been fully able to make and use other polynucleotides within the scope of the presently claimed invention.

Therefore, the rejection of claims 7-10, 22, 28, 29, 44, 45, 52, 61, and 68-72 as lacking enablement is improper and should be withdrawn.

The rejection of claim 27 under 35 U.S.C. § 112 (first paragraph) as lacking enablement for vector pET*dnaX* is respectfully traversed. The PTO has taken the position that the vector is not completely disclosed, because the complete nucleotide sequence is not defined in the specification. Applicants submit that this is unnecessary for enablement of the invention of claim 27. In particular, the pET16b vector used by applicants remains commercially available from Novagen (see attached Exhibit 1), and the specification discloses both the nucleotide sequence of a *Thermus thermophilus dnaX* (e.g., SEQ ID NO: 3, Figure 4C) and how one of skill in the art can insert a *Thermus thermophilus dnaX* nucleotide sequence into the pET16b vector (*see* Example 3 and accompanying Figure 9). Use of the vector for expression of a His-tagged tau subunit is described in Example 4. For this reason, one of skill in the art is fully able to make and use a pET*dnaX* expression vector. The rejection of claim 27 for lack of enablement should therefore be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: September 3, 2004

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9/3/04
Date

Wendy L. Barry

Amendments to the Drawings

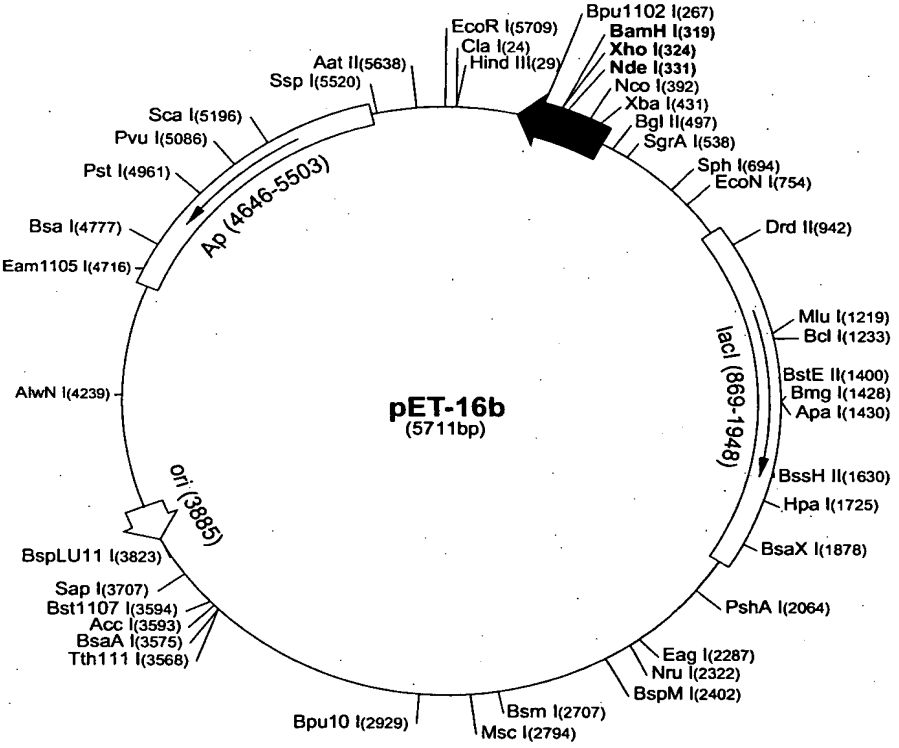
Enclosed as an attachment to this amendment is corrected Figure 4B. The corrections to this page include changes to the nucleotide numbering to correct a typographical error. Number '1820' in the original should have been '1800', and all subsequent numbers below are likewise off by a count of 20 bases.

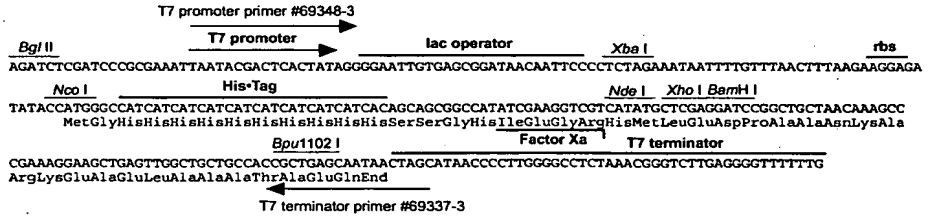
pET-16b Vector

TB046 2/00

The pET-16b vector (Cat. No. 69662-3) carries an N-terminal His•Tag® sequence followed by a Factor Xa site and three cloning sites. Unique sites are shown on the circle map. Note that the sequence is numbered by the pBR322 convention, so the T7 expression region is reversed on the circular map. The cloning/expression region of the coding strand transcribed by T7 RNA polymerase is shown below.

pET-16b sequence landmarks	
T7 promoter	466-482
T7 transcription start	465
His•Tag coding sequence	360-389
Multiple cloning sites	
(*Nde* I -*Bam*H I)	319-335
T7 terminator	213-259
lacI coding sequence	869-1948
pBR322 origin	3885
bla coding sequence	4646-5503





pET-16b cloning/expression region

pET-16b Restriction Sites

TB046 2/00

Enzyme	# Sites	Locations				
AatII	1	5638				
AccI	1	3593				
AceIII	7	986	1714	2045	3332	3473
		3775	5015			
AciI	89					
AflIII	2	1219	3823			
AluI	24					
AlwI	16					
Alw21I	8	719	1203	2526	2817	3641
		4141	5302	5387		
Alw44I	4	1199	3637	4137	5383	
AlwNI	1	4239				
ApaI	1	1430				
ApaBI	2	903	2400			
ApoI	2	1494	5709			
AvaI	2	324	2773			
AvaII	9	1771	2147	2235	2484	2787
		2829	3108	4854	5076	
BamHI	1	319				
BanI	12					
BanII	3	603	617	1430		
BbsI	5	1365	1704	2078	2941	5694
BbvI	28					
BccI	16					
Bce83I	7	208	2033	2203	3914	4212
		4453	5321			
BcefI	5	738	1079	1706	2515	4325
BcgI	8	1511	1545	2045	2079	3400
		3434	5221	5255		
BclI	1	1233				
BfaI	6	257	432	2837	4318	4571
		4906				
BglI	3	2283	2517	4836		
BglII	1	497				
BmgI	1	1428				
BpmI	6	1057	1546	2180	2734	3350
		4786				
Bpu10I	1	2929				
Bpu1102I	1	267				
BsaI	1	4777				
BsaAI	1	3575				
BsaBI	3	496	502	3020		
BsaHI	8	542	563	677	1176	1859
		2554	5253	5635		
BsaJI	11					
BsaWI	7	189	1538	2041	3012	4029
		4176	5007			
BsaXI	1	1878				
BsbI	2	3539	5259			
BscGI	13					
BsgI	3	1070	1270	2983		
BsiI	3	3996	5380	5687		
BsiEI	6	2004	2290	3739	4163	5086
		5235				
BsII	22					
BsmI	1	2707				
BsmAI	7	916	1321	1447	1834	3464
		4777	5553			
BsmBI	2	1834	3464			
BsmFI	4	680	2221	2446	3094	
BsoFI	52					
Bsp24I	12					
Bsp1286I	11					
BspEI	2	189	3012			
BspGI	3	2407	2484	3349		
BspLU11I	1	3823				
BspMI	1	2402				
BsrI	25					
BsrBI	3	452	3756	5557		
BsrDI	4	1266	1632	4777	4951	
BsrFI	8	160	529	538	905	2117
		2277	2631	4796		

Enzyme	# Sites	Locations				
BssHII	1	1630				
Bst1107I	1	3594				
BstEII	1	1400				
BstXI	3	1021	1150	1273		
BstYI	11					
Cac8I	41					
CjeI	26					
CjePI	28					
ClaI	1	24				
CviJI	96					
CviRI	26					
DdeI	11					
DpnI	29					
DraI	3	4582	4601	5293		
DrdI	2	3516	3931			
DrdII	1	942				
DsaI	3	392	656	2795		
EaeI	7	349	527	659	1893	2287
		2792	5104			
EagI	1	2287				
Eam1105I	1	4716				
EarI	3	837	3707	5511		
EciI	5	996	2743	3897	4043	4871
Eco47III	3	624	2125	3077		
Eco57I	2	4371	5383			
EcoNI	1	754				
EcoO109I	5	240	652	2787	2829	5692
EcoRI	1	5709				
EcoRII	10	129	942	1257	1797	1854
		2406	2789	3849	3970	3983
EcoRV	2	187	1669			
FauI	18					
FokI	14					
FspI	3	2706	2804	4938		
GdiII	6	349	527	659	1893	2287
		5104				
HaeI	8	947	2268	2340	2397	2794
		3838	3849	4301		
HaeII	13					
HaeIII	29					
HgaI	15					
HgiEII	2	817	4409			
HhaI	44					
Hin4I	5	16	1118	2489	4715	4789
HincII	2	1725	5257			
HindIII	1	29				
HinfI	14					
HpaI	1	1725				
HphI	17					
MaeII	12					
MaeIII	18					
MboII	15					
MluI	1	1219				
MmeI	2	4038	4222			
MnlI	34					
MscI	1	2794				
MseI	24					
MslI	10	1271	1559	1589	2379	2810
		3005	3396	4968	5127	5486
MspI	35					
MspA1I	11					
MwoI	44					
NarI	5	542	563	677	1859	2554
NciI	14					
NcoI	1	392				
NdeI	1	331				
NgoAIV	4	529	2117	2277	2631	
NlaIII	31					
NlaIV	28					
NruI	1	2322				
NspI	4	694	3168	3460	3827	
Pfl1108I	2	2106	4734			

Enzyme	# Sites	Locations				
PflMI	3	801	2669	2718		
PleI	7	480	768	855	1651	3717
		4202	4705			
PshAI	1	2064				
Psp5II	2	2787	2829			
Psp1406I	5	881	2249	3148	4942	5315
PstI	1	4961				
PvuI	1	5086				
PvuII	3	1819	1912	3414		
RcaI	4	617	4543	5551	5656	
RsaI	4	165	1366	3629	5196	
SapI	1	3707				
Sau96I	22					
Sau3AI	37					
ScaI	1	5196				
ScrFI	24					
SfaNI	24					
SfcI	5	138	465	4088	4279	4957
SgrAI	1	538				
SphI	1	694				
SspI	1	5520				
StyI	3	244	392	2717		
TaqI	14					
TaqII	8	1127	1345	2018	3725	5064
		5249	5402	5419		
TfiI	7	1898	2200	2354	2652	2873
		3377	3798			
ThaI	39					
TseI	28					
Tsp45I	9	124	1400	2228	2495	3262
		3475	3570	4972	5183	
Tsp509I	16					
Tth111I	1	3568				
Tth111II	7	1058	1751	3284	4413	4420
		4452	5708			
UbaJI	24					
VspI	4	480	1904	1963	4888	
XbaI	1	431				
XcmI	3	1075	1591	1609		
XhoI	1	324				
XmnI	2	3381	5315			

Enzymes that do not cut pET-16b:

AflII	AgeI	AscI	AvrII	BaeI
BseRI	BsrGI	Bsu36I	DraIII	FseI
KpnI	MunI	NheI	NotI	NsiI
NspV	PacI	PmeI	PmlI	RleAI
RsrII	SacI	SacII	SalI	SexAI
SfiI	SgfI	SmaI	SnaBI	SpeI
SrfI	Sse8387I	StuI	SunI	SwaI